Article

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Comparative Accuracy and Cost-Effectiveness of Dynamic Contrast Enhanced Computed Tomography and Positron Emission Tomography in the Characterisation of Solitary Pulmonary Nodules

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Abstract

Introduction:

Dynamic contrast-enhanced computed tomography (DCE-CT) and Positron Emission Tomography/Computed Tomography (PET/CT) have a high reported accuracy for the diagnosis of malignancy in solitary pulmonary nodules. The aim of this study was to compare the accuracy and cost-effectiveness of these.

Methods:

In this prospective multicentre trial, 380 participants with a solitary pulmonary nodule (8-30mm) and no recent history of malignancy underwent DCE-CT and PET/CT. All patients underwent either biopsy with histological diagnosis or completed CT follow-up. Primary outcome measures were sensitivity, specificity, and overall diagnostic accuracy for PET/CT and DCE-CT. Costs and cost-effectiveness were estimated from a healthcare provider perspective using a decision-model.

Results:

312 participants (47% female, 68.1±9.0 years) completed the study, with 61% rate of malignancy at 2 years. The sensitivity, specificity, positive predictive value and negative predictive values for DCE-CT were 95.3% [95% CI 91.3;97.5], 29.8% [95% CI 22.3;38.4], 68.2% [95% CI 62.4%;73.5%] and 80.0% [95% CI 66.2;89.1] respectively, and for PET/CT were 79.1% [95% CI 72.7;84.2], 81.8% [95% CI 74.0;87.7], 87.3%[95% CI 81.5;91.5) and 71·2% [95% CI 63.2;78.1]. The area under the receiver operator characteristic curve (AUROC) for DCE-CT and PET/CT was 0.62 [95%CI 0.58;0.67] and 0.80 [95%CI 0.76;0.85] respectively ($p<0.001$). Combined results significantly increased diagnostic accuracy over PET/CT alone (AUROC=0.90 [95%CI 0.86;0.93], $p<0.001$). DCE-CT was preferred when the willingness to pay per incremental cost per correctly treated malignancy was below £9000. Above £15500 a combined approach was preferred.

Conclusions:

PET/CT has a superior diagnostic accuracy to DCE-CT for the diagnosis of solitary pulmonary nodules. Combining both techniques improves the diagnostic accuracy over either test alone and could be cost-effective. (Clinical trials.gov - NCT02013063).

Key words

Solitary Pulmonary Nodule; Positron Emission Tomography Computed Tomography; Tomography, X-Ray Computed; Diagnostic Test Accuracy; Costs and Cost Analysis

Key Messages

What is the key question?

Which out of dynamic contrast enhanced CT (DCE-CT) and PET/CT is the most accurate and cost effective approach to the diagnosis of solitary pulmonary nodules between 8 and 30mm in size.

What is the bottom line?

While DCE-CT is more sensitive, PET/CT has higher overall accuracy for the characterisation of solitary pulmonary nodules. Combining the metabolic and perfusion data from the two techniques may be more accurate and cost-effective.

Why read on?

Solitary pulmonary nodules form an opportunity to treat cancer at a potentially curative stage, however only a minority of nodules will be malignant. A cost effective and accurate technique is required to detect those that require treatment.

Introduction

Despite a declining incidence in many first world countries, lung cancer remains the leading cause of cancer related death worldwide [1]. A proportion of patients with lung cancer present with a solitary pulmonary nodule (SPN) on diagnostic imaging tests, which represents an important group of patients as it represents early disease with excellent survival rates following radical treatment[2]. However, not all SPNs are due to lung cancer and the accurate characterisation of SPNs is an on-going diagnostic challenge with significant associated health costs. With the advent of national lung cancer screening programs, the number of patients with a SPN requiring further investigation will increase substantially [3].

Due to the association between nodule size and likelihood of malignancy, current management strategies are directed by nodule size. Nodules <5mm require no follow-up, while nodules ≥8mm in diameter require further diagnostic work-up with ^{18}Fluorine Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) or biopsy [4]. However, both procedures are not without limitations; biopsy is invasive and PET/CT is expensive and has limited availability. Dynamic contrast-enhanced computed tomography (DCE-CT) allows quantification of the enhancement of pulmonary nodules following administration of intravenous iodine-based contrast material[5]. The enhancement reflects the extent of vascularity with high sensitivity and moderate specificity for the diagnosis of SPNs [6]. DCE-CT may be a more cost-effective approach in the diagnostic work-up of nodules than PET/CT [7] although this evidence is weak. The studies were predominantly single-centred, did not directly compare PET with DCE-CT, included pulmonary masses as well as nodules, or used older PET technology with poor spatial resolution[7,8]. The British Thoracic Society (BTS) guidelines called for further comparative studies comparing PET/CT with DCE-CT before it can be considered as a viable alternative [4].

This multicentre trial compares the diagnostic accuracy and cost-effectiveness of DCE-CT with PET/CT in the assessment of solitary pulmonary nodules.

Materials and Methods

This prospective multicentre observational study assesses the diagnostic performance and incremental value of DCE-CT, compared with PET/CT in a cohort of patients with SPN in accordance with the guidance for the methods of technology appraisal issued by NICE [9]. The full trial protocol has been published [10] and registered on Clinical trials.gov (NCT02013063). The SPUtNIk Trial was approved by the South West Research Ethics Committee Centre (12/SW/0206, UK). All participants provided written informed consent.

Settings and participants

Participants with a SPN were recruited from secondary and tertiary outpatient settings at 16 hospitals within the UK. Inclusion criteria were: Soft tissue solitary dominant pulmonary nodule of ≥ 8mm and ≤30mm on axial plane measured on lung window using conventional CT scan with no other ancillary evidence strongly indicative of malignancy (e.g. distant metastases or unequivocal local invasion); >18 years of age. Presence of other small lesions <4mm that would normally be disregarded, meant the patient could be included. Exclusion criteria were: Pregnancy; History of malignancy within the past 2 years; Confirmed aetiology of the nodule at the time of qualifying CT scan; Biopsy of nodule prior to DCE-CT scan; Contra-indication to imaging examinations, potential radiotherapy or surgery.

Recruited patients underwent a PET/CT and DCE-CT to assess their pulmonary nodules. PET/CT and DCE-CT scans were ideally performed within 14 days, with up to 21 days allowed between scans when sites had difficulty with scheduling. Following the PET/CT and DCE-CT investigations, management of the SPN was directed by the local/specialist lung multidisciplinary team meeting (MDT).

Objectives

The primary objective of the trial was to determine the diagnostic performances and cost-effectiveness of DCE-CT and PET/CT for the characterisation of SPNs. The secondary objectives were to assess whether combining DCE-CT with PET/CT is more accurate and/or cost-effective, in the characterisation of SPNs, than either test used alone or in series.

PET/CT

All 25 PET/CT scanners (Supplementary Material) underwent baseline accreditation and annual quality assurance testing by the UK PET Core Lab [11]. All PET/CTs were reported by accredited PET/CT reporters, blind to the histology results. The CT features were graded as: 0 - Round, well-defined lesion with laminated or popcorn calcification; 1 = Inflammatory features e.g. air bronchograms, enfolded lung; 2 = Smooth well-defined margins, uniform density; 3 = Lobulated, spiculated or irregular margins; 4 = Evidence of distant metastases (i.e. M1 disease). The PET features were graded as 0 = No visible uptake; 1 = Uptake less than mediastinal blood pool; 2 = Uptake comparable to mediastinal blood pool; 3 = Uptake greater than mediastinal blood pool; 4 = Evidence of distant metastases (i.e. M1 disease). The maximum standardised uptake value (SUVmax) was also recorded. The combined PET/CT assessment was classified as positive for malignancy if one of the following criteria were met: Grade 4 on PET or CT, Grade 3 on PET and ≥ Grade 2 on CT, or Grade 2 on PET and ≥Grade 3 on CT. For SUVmax analysis, an uptake ≥2·5 was considered positive for malignancy.

DCE-CT

The CT scans were acquired on 16 scanners (Supplementary material). The protocol for performing and analysing the DCE-CT has been reported previously [12]. Following a bolus of 1·4 ml/kg iodinated contrast material (300 mg/ml) injected intravenously at 2ml/sec, images were acquired at 100kV at 0s, 60s, 120s, 180s and 240s and reported by local trained physicians. For each time point, the attenuation of the nodule was measured in Hounsfield units (HU) by placing a region of interest (ROI) occupying approximately 70% of the nodule's diameter. All attenuation analyses were performed in the axial plane using mediastinal windows. Maximum nodule enhancement was calculated as: highest post contrast attenuation value - baseline attenuation. A Peak Enhancement (PE) ≥20HU was considered positive for malignancy.

Outcomes

The primary outcomes were the comparative diagnostic accuracy of DCE-CT and PET/CT, and the cost-effectiveness of their implementation within the diagnostic work-up pathway for SPNs.

For the diagnostic accuracy, the reference standard was histological diagnosis, or MDT decision at 2 years follow-up. In the absence of histological diagnosis, assessment is based on nodule growth as per BTS guidelines (nodule growth is defined as an increase in its diameter or volume of ≥ 25%) [4]. Stability of nodule size was regarded as an indication of benign diagnosis following completion of 2 years CT follow up for 2D measurements or 1 year for 3D volumetric monitoring [4]. This reference standard was performed blind to the DCE-CT results, but not to the results of the PET/CT which was performed as part of the clinical care. The participants' clinical notes were reviewed at 24 months to determine patient management including investigative procedures, surgical interventions, treatment and associated inpatient stays.

Sample size calculation

At study inception 375 participants was considered an adequate number for the study to be informative, whilst still being achievable within a reasonable timeframe. Published sensitivity for PET/CT varies between 77 and 96% (pooled weighted average: 92%) with specificity between 76 and 100% (pooled weighted average: 90%) [5]. Published sensitivity and specificity values for DCE-CT vary between 81 and 100% (pooled weighted average: 87%) and 29 and 100% (pooled weighted average: 83%) respectively [5,6,13,14]. The mean prevalence of malignancy in indeterminate SPN has been reported as 68·5% [7]. At this prevalence, a sample size of 375 would produce 257 malignant and 118 benign SPNs. This will give confidence limits for sensitivity and specificity of DCE-CT of 87% ± 4·1% and 83% ± 6·8% and PET/CT of 92% ± 3·3% and 90% ± 5·4% respectively.

When considering the accuracy of both tests in combination, those with a negative DCE-CT are classed as benign, while a positive DCE-CT progressed to PET/CT. If the PET/CT was positive the nodule was classed as 'malignant' and those PET/CTs which were negative were

classed as 'benign'. The specificity of this process is the same as using PET/CT alone but we need to estimate the sensitivity. Based on previous data of 130 malignant tumours, 114 were both DCE-CT and PET/CT positive. This suggests the sensitivity of the joint testing procedure is 114 / 130 = 0·877. Compared to the PET/CT sensitivity of 0·92, the joint testing approach is projected to reduce sensitivity by about 4%. A total sample size of 288 patients is required (including 197 with malignant tumours) to detect a 4% reduction in sensitivity for the combined approach compared to PET/CT alone.[15] This calculation assumes an 80% power, 5% significance level and prevalence of malignancy of 0·685.

Statistical analysis - Accuracy

We considered the diagnostic accuracy of positive PET/CT and DCE-CT, both separately and in conjunction, in relation to a diagnosis of lung cancer by 2 years. The diagnostic accuracy of the tests was assessed by sensitivity, specificity, and overall diagnostic accuracy using the pre-specified classifications (including the combination of tests) and cut-offs. Further exploratory analyses were performed considering the full spectrum of cut-offs using SUVmax and PE separately and in combination using logistic regression. Receiver operator characteristic curves were constructed for these exploratory analyses and an optimal cut-point keeping the sensitivity above 90% and maximising specificity within this limitation was examined, as was an alternative cut-point that provided the best trade off in sensitivity and specificity.

Economic evaluation

A decision analytic model (Supplementary Figure S1) on which the cost-consequence and cost-effectiveness analyses were based, was developed to synthesize evidence and estimate the expected costs and consequences of each imaging strategy for a cohort of people aged 68 years, presenting with a SPN (8-30mm) and managed according to the imaging test result. The time horizon of the model was two-years but life-expectancy and quality adjusted life years (QALYs) were extrapolated over the patient lifetime.

Imaging test accuracy and probabilities of following different management pathways were sourced from the trial, the literature, and clinical expert opinion. Cost estimates were derived from routine sources (i.e. NHS reference costs, etc) as well as from the literature

and were inflated where necessary, to 2018 prices. Further evidence required to estimate life expectancy and health related quality of life were sourced from the literature. The data used in the economic model are reported in Supplementary Tables S9-S13.

Parameter uncertainty within the model was addressed using probabilistic sensitivity analysis. Multiple variable one-way sensitivity was also used to identify those parameters to which costs and the proportion of accurately treated cases and malignancies were most sensitive to. Scenario analyses explored the impact of structural assumptions (i.e. exclusion of indeterminate results) on the costs and consequences. Model validation involved the comparison of results to an independent model, developed to answer the same decision question using different software by other members of the study team.

Results

Of the 2541 patients screened (*Figure 1*) 19% (n=413) had more than one nodule, 14% (n=296) declined, 14% (n=306) had a nodule out size range and 12% (n=264) had malignancy within the last two years. Of the 380 patients recruited, 312 (53% male, median age of 69 years, IQR = 62 to 74, range = 35 to 89) completed both DCE-CT and PET/CT examinations and 2 years of follow-up and comprise the dataset for analysis (See Table 1 for Baseline characteristics). Ex-smokers accounted for 57% with 25% still smoking. The median pulmonary nodule diameter on baseline CT was 15mm (IQR = 12-20).

Lung cancer was confirmed in 191/312 (61%) participants (*Table 2).* The commonest cancer type was non-small cell lung cancer (145/191, 76%). Of these, the most common subtypes were adenocarcinoma (107/145, 74%) and squamous cell carcinoma (30/145, 21%). In 20 cases, it was not possible to achieve a histological diagnosis due to co-morbidities and therefore an MDT decision based on clinical and radiological diagnosis was made. In 11 of these cases, treatment with stereotactic ablative radiotherapy (SABR) was undertaken. Benign disease was diagnosed in 121/312 participants. This was confirmed by biopsy in 27 cases and using up to two years CT follow-up in 94 patients.

Of the 312 participants 49% had their DCE-CT on the same day as their PET/CT, 90% within two weeks (median delay = 1 day, IQR 0 to 8, range = 0 to 32 days) and 98% within three weeks. On the baseline PET/CT and DCE-CT the majority of the nodules were classified as Grade 3 (Table 3). On PET/CT 161 (52%) had ^{18}F-FDG uptake greater than the mediastinal blood pool (grade 3), 10% had similar uptake (grade 2), 21% had uptake less than the mediastinal blood pool (grade 1) and 17% had no uptake (grade 0). The mean of the SUVmax was 4·75±5.65 (Range: 0-35·3). There was lymph node involvement in 40 (13%) cases and 4 (1%) were found to have metastatic disease. On DCE-CT the mean Peak Enhancement (PE) was 48·6±28.3 HU (Range 0-179), with a PE ≥ 20 HU reached in 267 (86%) of patients.

The sensitivity, specificity, positive predictive value and negative predictive values for DCE-CT were 95.3% [95% CI 91.3;97.5], 29.8% [95% CI 22.3;38.4], 68.2% [95% CI 62.4%;73.5%]

and 80.0% [95% CI 66.2;89.1] respectively, and for PET/CT were 79.1% [95% CI 72.7;84.2], 81.8% [95% CI 74.0;87.7], 87.3%[95% CI 81.5;91.5) and 71·2%
[95% CI 63.2;78.1].

The sensitivity, specificity, positive predictive value and negative predictive values for DCE-CT was 95·3% (95% CI 91·3;97·5), 29·8% (95% CI 22.3;38·4), 68.2% [95% CI 62.4%;73.5%] and 80.0% [95% CI 66.2;89.1] respectively, and for PET/CT grade was 79·1% (95% CI 72·7;84·2), 81·8% (95% CI 74·0;87·7), 87.3%[95% CI 81.5;91.5) and 71·2% [95% CI 63.2;78.1] (Table 4). Using an SUVmax of ≥2·5 as a cut-off, the sensitivity and specificity was 76·4% (95% CI 69·9;81·9) and 81·5% (95% CI 73·6;87·5) respectively. When combining DCE-CT with PET/CT (Table 4) the performance is similar to PET/CT alone, but with a slightly lower sensitivity of 75·4% and a slightly higher specificity of 83·5%.

Figure 2 shows Receiver Operating Characteristic (ROC) curves for the pre-specified rules and the best performing combinations following exploratory modelling with logistic regression using the key elements from the imaging scans. The area under the receiver operator characteristic curve (AUROC) was 0·62 (95% CI 0·58;0·67) for DCE-CT and 0·80 (95%CI 0·76;0·85) for PET/CT ($p<0.0001$ for difference). SUVmax ≥2·5 as a cut off was no more accurate than the combined PET/CT grading (AUROC 0·79 (95% CI 0·74;0·84), $p=0.48$ for difference). Exploratory modelling of the various parameters at different thresholds showed SUVmax had the best diagnostic accuracy with an AUROC of 0·87 (95% CI 0·83;0·91). Addition of CT grade to DCE-CT PE slightly increased the accuracy of DCE-CT from an AUROC of 0.74 (95% CI 0.68 to 0.80) for PE alone, to an AUROC of 0.77 (95% CI 0.71 to 0.83) for combined grade and PE, but this remained lower than that of PET/CT. Combining DCE-CT PE with SUVmax provided the best accuracy with an AUROC of 0·90 (95% CI 0·86;0·93, $p=0.029$ versus SUVmax alone).

The single best cut-off options for the exploratory models are in *Table 5* (including both a 90% minimum sensitivity cut point and a balanced sensitivity and specificity cut point). Using an SUV threshold of ≥ 2·3 produces an increased performance of 80.5% sensitivity, 78.2% specificity, 71·5% NPV, and 85·5% PPV. Using a threshold probability of ≥ 0·53

produces 84·7% sensitivity, 77·3% specificity, 76·0% NPV, and 85·6% PPV for the model combining SUVmax and DCE-CT PE

Cost-consequence analysis showed DCE-CT was on average least costly (£3,305 [95% CI £2,952;£3,746]) compared with PET/CT (£4,013 [95% CI £3,673;£4,498]) or combined DCE-CT & PET/CT (£4,058 [95% CI £3,702;£4,547]) (see also *Table 6*). PET/CT resulted on average in more correctly managed malignant cases than DCE-CT (44% [95% CI 39%;49%] vs. 40% [95% CI 35%;45%]) and the combination improved this proportion (47% [95% CI 42%;51%]). PET/CT resulted on average in more appropriately managed cases compared with DCE-CT for overall management (82% [95% CI 79%;85%] vs. 78% [95% CI 74%;82%]), life expectancy (10.50 years [95% CI 9.91;11.15] vs. 10.22 years [95% CI 9.60;10.91]), QALYs (7.64 [95% CI 7.19;8.15] vs. 7.43 [95% CI 6.94;7.96]), and the proportion of patients receiving delayed treatment (20% [95% CI 17%;24%] vs. 26% [95% CI 21%;30%]). The combination further improved outcomes compared to PET/CT (Table 6).

The incremental cost per malignant case treated was £11,395 for the comparison of the combined approach (DCE-CT / PET/CT) compared with DCE-CT. The incremental cost per correctly managed case was similarly £11,323. These values do not reflect statistical imprecision and the likelihood that DCE-CT, PET/CT and a combined approach might be considered cost-effective at different threshold values for society's willingness to pay for a malignant case treated, and a correctly managed case are presented in Figure 3A and B respectively. PET/CT was unlikely to be considered cost-effective. DCE-CT was most likely cost-effective when the willingness to pay (WTP) ceiling ratio per correctly managed case was below £11,395. Above £16,000 a combined approach would be cost-effective. When society is willing to pay no more than £9000 per correctly treated malignancy DCE-CT was preferred. Above £15,500 the combined approach was cost-effective.

Discussion

In this multicentre trial we have found that: (1) PET/CT is more accurate than DCE-CT for the diagnosis of solitary pulmonary nodules; (2) combining perfusion data from DCE-CT and metabolic data from PET may yield a more accurate assessment of the nodule than either alone; (3) This combined approach is the most cost effective at higher willingness to pay thresholds.

The strengths of this study are that it is the largest diagnostic accuracy study of PET/CT for the diagnosis of SPNs, the second largest study of the diagnostic accuracy of DCE-CT, and the only multicentre, multivendor study directly comparing the two techniques making the results more precise and generalizable than previous work. The sensitivity and specificity for PET/CT were 79·1% (95% CI 72·7;84·2) and 81·8% (95% CI 74·0;87·7) similar to the meta-analysis of 21 studies with 1,557 nodules, where the pooled sensitivity was 89% (95% CI 87;91) and specificity of 70% (95% CI, 66;73) [16]. The lower sensitivity but higher specificity reflects the use of PET/CT grading rather than SUVmax in SPUTNIK with the CT grading improving the specificity [17]. In this meta-analysis [16], many studies were retrospective and used an infrequently pre-defined SUVmax cut-off point which may have overly optimised sensitivity. Our exploratory analysis reinforces that if an optimised SUVmax is used rather than the PET/CT grading, the sensitivity is 91.0% (95% CI 86·1;94·3) and specificity was 63.0% (54·1;71·2), closer matching the meta-analysis.

In our study, DCE-CT had the higher sensitivity of 95·3% with the penalty of low specificity of 29·8%. Compared to a pooled sensitivity and specificity of 95% and 76% in a recent meta-analysis of DCE-CT (23 studies with 2397 participants)[18], our cohort study had much lower specificity and the reasons for this are not clear. The closest results to our own come from Swensen et al., who examined the diagnostic accuracy of DCE-CT in 356 patients across 7 sites, finding a sensitivity of 98% and specificity of 58% using a threshold of 15HU [14] and the largest DCE-CT study with 486 patients with sensitivity and specificity of 98% and 46% respectively [19]. This latter study demonstrated that using both wash-in and wash-out kinetics improved the specificity of DCE-CT with minimal impact on sensitivity, but imaged out to 5 minutes providing more time for contrast to wash out. Future studies focusing on

adding wash-out and the nodule characteristics to DCE-CT alongside volumetric analysis will be useful to determine if these may improve the diagnostic performance of this technique.

Our findings support the BTS and Fleischner guidelines, which recommend biopsy or PET/CT for nodules 8-30mm in diameter [4,20]. When considering access and cost, DCE-CT is the most cost-effective approach due to a lower unit price similar to a health economic analysis performed by Gould et al [8]. However, this strategy results in a lower number of correctly treated cases. At higher willingness to pay thresholds, DCE-CT followed by PET/CT if positive, becomes the most cost-effective strategy. DCE-CT can be performed during the initial CT if a nodule is found and indeed many institutes conduct an adaptive imaging strategy during CT examinations. Such a practice would have substantial benefits for the patient, minimising additional hospital visits and making the initial CT more accurate. Orlacchio et al. have previously demonstrated the feasibility of incorporating DCE-CT at the end of the PET image acquisition reducing the need for multiple visits and appointments [21].

However, it is important to be cautious as the difference in costs between PET/CT alone and a combination of DCE-CT and PET/CT was small on average and may lack economic significance. The combination of DCE-CT and PET/CT was the best alternative strategy when comparing patient outcomes, correctly identifying the highest proportion of patients with malignant disease (46·7%), the lowest proportion of malignant cases left without treatment (13·7%), and achieved the lowest proportion of inappropriate treatment in patients with a benign nodule (9·0%). These results led to the appropriate management of 84·4% of patients.

A limitation of this study is the applicability of our results to SPNs found at lung screening, a setting where the prevalence of malignancy appears to be lower (National Lung Screening Trial 15·0% malignancy in 10-30mm nodules and NELSON trial 15·2% malignancy in nodules >10mm) [22,23]. The 61% malignancy rate of nodules in this study represents indeterminate SPNs found in normal clinical practice and is in keeping with previous meta-analyses of MRI and PET in SPNs [16,24]. Previous work has shown the sensitivity of a technique to be relatively robust to disease prevalence and for the specificity to increase with falling prevalence [25]. Therefore, it can be postulated that the diagnostic accuracy of the techniques would be

similar, or even improved, in a screening population. However, this requires further prospective evaluation in a screening detected cohort. The current study had a low rate of diagnosis of infectious diseases as the underlying aetiology of the nodules, thus the accuracy and thresholds may not be translatable to environments where such conditions are more endemic. Finally, only solid or part solid nodules were included in the current study where the solid component was sufficient to allow for PET and DCECT quantification. As a result the findings cannot be extrapolated to ground glass nodules nor part-solid nodules with minimal solid component.

In conclusion, while DCE-CT is more sensitive, PET/CT has significantly higher overall accuracy for the characterisation of solitary pulmonary nodules. Combining the metabolic and perfusion data from the two techniques may be more accurate still and could be cost-effective.

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Data sharing:

Individual participant data will be made available, including data dictionaries, for approved data sharing requests. Individual participant data will be shared that underlie the results reported in this article, after de-identification and normalisation of information (text, tables, figures, and appendices). The study protocol and statistical analysis plan will also be available. Anonymous data will be available for request from three months after publication of the article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate, signed a Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation, covering SCTU conditions for sharing and if required, an additional Data Sharing Agreement from Sponsor. Proposals should be directed to ctu@soton.ac.uk.

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TABLES

Table 1: Baseline characteristics and Medical History of the study participants (n=312)

Variable (unit)*		**Number (percentage)**
Gender	Male	165 (53%)
	Female	147 (47%)
Age (years)	Mean± SD	68·1 ± 8·95
Smoking status	Never-smoker	57 (19%)
	Ex-smoker	170 (56%)
	Current smoker	77 (25%)
	Missing	8
Location of SPN	Left Lower Lobe	51 (16%)
	Left Upper Lobe	78 (25%)
	Right Lower Lobe	73 (23%)
	Right Middle Lobe	21 (7%)
	Right Upper Lobe	89 (29%)
WHO Performance status grade[26]	0:	151 (49%)
	1:	133 (43%)
	2:	22 (7%)
	3:	5 (2%)
	Missing	1
Medical History of Cardiovascular Disease	**Any Cardiovascular Disease**	**70 (23%)**
	Missing	11
	Ischaemic Heart Disease	51 (17%)
	Valve Disease	11 (4%)
	Cardiomyopathy	2 (1%)
Medical History of Respiratory Disease	**Any Respiratory Disease**	**126 (41%)**
	Missing	5
	COPD	90 (29%)
	Asthma	29 (9%)
	Pulmonary Fibrosis	6 (3%)
	Other ILD	0 (0%)
	Other	17 (6%)
Medical History of Inflammatory Disease	**Any Inflammatory Disease**	**65 (21%)**
	Missing	4
	Rheumatoid	20 (6%)
	Wegener's	1 (0%)
Medical History of Infectious Disease	**Any Infectious Disease**	**112 (37%)**
	Missing	6
	Histoplasmosis	1 (0%)
	Chicken Pox	108 (35%)
	Tuberculosis	9 (3%)

Variable (unit)*		Number (percentage)
Previous Inhalational Exposures	**Any Previous Exposure**	**63 (21%)**
	Missing	14
	Asbestos	55 (18%)
	Coal	14 (5%)
	Silica	4 (1%)
Prior Malignancy	**Any Prior Malignancy**	**38 (12%)**
	Missing	6

Abbreviations: SD= standard deviation, SPN=solitary pulmonary nodule.

*Subgroups may add to more than the Group totals as patients may have more than one condition within any disease grouping

Table 2: Final Nodule Diagnosis in the study cohort, further divided by smoking status (n=312)

Two-year malignancy status	Classification of nodule	Never smokers	Ex-Smokers	Current Smokers	Total (%)
Malignant (N=191)	**Non-Small cell lung cancer**	**15 (56%)**	**78 (76%)**	**47 (82%)**	**145 (76%)**
	Adenocarcinoma	14 (93%)	55 (71%)	34 (72%)	107 (74%)
	Squamous cell carcinoma	0 (0%)	20 (26%)	10 (21%)	30 (21%)
	Large cell undifferentiated	1 (7%)	0 (0%)	1 (2%)	2 (1%)
	Not otherwise specified	0 (0%)	3 (4%)	2 (4%)	6 (4%)
	Carcinoid tumour	**8 (30%)**	**4 (4%)**	**0 (0%)**	**12 (6%)**
	Small cell lung cancer	**0 (0%)**	**6 (6%)**	**1 (2%)**	**7 (4%)**
	Radiological diagnosis only*	**0 (0%)**	**13(7%)**	**7 (4%)**	**20 (5%)**
	Other	**4 (15%)**	**1 (1%)**	**1 (2%)**	**6 (3%)**
	No further information provided	**0 (0%)**	**0 (0%)**	**1 (2%)**	**1 (1%)**
Benign (N=121)	**Benign nodule not otherwise specified**	**17 (57%)**	**36 (53%)**	**7 (35%)**	**61 (50%)**
	Hamartoma	**7 (23%)**	**13 (19%)**	**5 (25%)**	**26 (21%)**
	Infection / Inflammation	**3 (10%)**	**15 (22%)**	**5 (25%)**	**24 (20%)**
	Other	**1 (3%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**
	No further information provided	**2 (7%)**	**4 (6%)**	**3 (15%)**	**9 (7%)**

* Includes those undergoing Stereotactic ablative radiotherapy based on radiology alone

Table 3: Initial CT, DCE-CT and PET/CT scan information (n=312)

Scan	Variable (units)		Number (percentage)
Baseline CT	Grade of SPN	0:	5 (2%)
		1:	10 (3%)
		2:	59 (20%)
		3:	212 (74%)
		4:	2 (1%)
		Missing	24
	Lymph Nodes enlarged	No	288 (92%)
		Yes	24 (8%)
		Missing	0
	Evidence of Metastatic disease	No	309 (100%)
		Yes	0 (0%)
		Missing	3
PET/CT	SUVmax	Mean (SD)	4·91 (5·65)
		Missing	2
	Grade of SPN on CT	0:	6 (2%)
		1:	13 (4%)
		2:	66 (22%)
		3:	208 (71%)
		4:	2 (1%)
		Missing	17
	Grade of SPN on PET	0:	52 (17%)
		1:	67 (21%)
		2:	30 (10%)
		3:	161 (52%)
		4:	2 (1%)
		Missing	0
	Reporter Diagnosis of SPN	Cancer	90 (29%)
		Indeterminate	191 (61%)
		Non-cancer	31 (10%)
	Diagnosis of SPN according to Protocol	Cancer	161 (52%)
		Non-cancer	151 (48%)
	Lymph Nodes affected	No	269 (87%)
		Yes	40 (13%)
		Missing	3
	Evidence of Metastases	No	306 (99%)
		Yes	4 (1%)
		Missing	2
DCE-CT	Peak Enhancement	Mean ± SD	48·6 ± 28·3

Table 3: Initial CT, DCE-CT and PET/CT scan information (n=312)

Scan	Variable (units)		Number (percentage)
	Grade of SPN	0:	3 (1%)
		1:	12 (4%)
		2:	63 (21%)
		3:	223 (74%)
		4:	0 (0%)
		Missing	10
	Radiologists Diagnosis of SPN	Cancer	51 (17%)
		Indeterminate	227 (73%)
		Non-cancer	31 (10%)
		Missing	3
	Diagnosis according to peak enhancement ≥15HU	Cancer	281 (90%)
		Non-cancer	31 (10%)
	Diagnosis according to peak enhancement ≥ 20 HU	Cancer	267 (86%)
		Non-cancer	45 (14%)

Abbreviations: SPN= solitary pulmonary nodule, CT= Computed tomography, DCE-CT= dynamic contrast-enhanced computed tomography , PET/CT=18Fluorine Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, SUVmax= maximum standardised uptake value, HU= Hounsfield unit.

Table 4: Diagnostic performance of each Imaging technique using the predefined thresholds (N=312)

	Imaging Technique	Sensitivity (95% CI)	Specificity (95% CI)	Negative Predictive value (95% CI)	Positive Predictive value (95% CI)	Overall Diagnostic Accuracy (95% CI)
Primary Outcomes	DCE-CT (Peak enhancement ≥ 20)	182/191 - 95·3% (91·3% to 97·5%)	36/121 - 29·8% (22·3% to 38·4%)	36/45 - 80·0% (66·2% to 89·1%)	182/267 - 68·2% (62·4% to 73·5%)	218/312 – 69·9% (64·6% to 74·7%)
	PET/CT (Based on PET and CT grading)	151/191 – 79·1% (72·7% to 84·2%)	99/121 – 81·8% (74·0% to 87·7%)	99/139 – 71·2% (63·2% to 78·1%)	151/173 – 87·3% (81·5% to 91·5%)	250/312 – 80·1% (75·4% to 84·2%)
Secondary Outcomes	PET/CT (N=310) (Based on an SUV maximum ≥ 2·5)	146/191 – 76·4% (69·9% to 81·9%)	97/119 – 81·5% (73·6% to 87·5%)	97/142 – 68·3% (60·3% to 75·4%)	146/168 – 86·9% (81·0% to 91·2%)	243/310 – 78·4% (73·5% to 82·6%)
	Combination of DCE-CT and PET/CT*	144/191 - 75·4% (68·8% to 81·0%)	101/121 - 83·5% (75·8% to 89·0%)	101/148 - 68·2% (60·4% to 75·2%)	144/164 - 87·8% (81·9% to 92·0%)	245/312 – 78·5% (73·6% to 82·7%)

Abbreviations: DCE-CT= dynamic contrast-enhanced computed tomography , PET/CT=18Fluorine Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, CI= Confidence interval.

*Where if DCE-CT is negative the nodule is considered benign, while if it is positive it progresses to PET/CT with adjudication then based upon the PET/CT grading

Table 5: Diagnostic performance of the best performing Exploratory models (N=312)

Rule	Imaging Technique	Sensitivity (95% CI)	Specificity (95% CI)	Negative Predictive value (95% CI)	Positive Predictive value (95% CI)	Overall Diagnostic Accuracy (95% CI)
At least 90% Sensitivity (where possible)	SUVmax (N=309) (Positive if ≥ 1·8)	173/190 – 91·0% (86·1% to 94·3%)	75/119 – 63·0% (54·1% to 71·2%)	75/92 – 81·5% (72·4% to 88·1%)	173/217 – 79·7% (73·9% to 84·5%)	248/309 – 80·3% (75·5% to 84·3%)
	DCE-CT Peak Enhancement (Positive if ≥ 25) (N=311)	176/190 – 92·6% (88·0% to 95·6%)	47/121 – 38·8% (30·6% to 47·7%)	47/61 – 77·1% (65·1% to 85·8%)	176/250 – 70·4% (64·5% to 75·7%)	223/311 – 71·7% (66·5% to 76·4%)
	SUVmax and DCE-CT Peak enhancement (Positive if Probability ≥ 0·43) (N=308)	171/189 – 90·5% (85·5% to 93·9%)	82/119 – 68·9% (60·1% to 76·5%)	82/100 – 82·0% (73·3% to 88·3%)	171/208 – 82·2% (76·4% to 86·8%)	253/308 – 82·1% (77·5% to 86·0%)
Best Balance of Sensitivity and Specificity	SUVmax (N=310) (Positive if ≥ 2·3)	153/190 – 80·5% (74·3% to 85·5%)	93/119 – 78·2% (69·9% to 84·6%)	93/130 – 71·5% (63·3% to 78·6%)	153/179 – 85·5% (79·6% to 89·9%)	246/309 – 79·6% (74·8% to 83·7%)
	DCE-CT Peak Enhancement (Positive if ≥ 38·5) (N=311)	147/190 – 77·4% (70·9% to 82·7%)	80/121 – 66·1% (57·3% to 73·9%)	80/123 – 65·0% (56·3% to 72·9%)	147/188 – 78·2% (71·8% to 83·5%)	227/311 – 73·0% (67·8% to 77·6%)
	SUVmax and DCE-CT Peak Enhancement (Positive if Probability ≥ 0·53) (N=308)	160/189 – 84·7% (78·8% to 89·1%)	92/119 – 77·3% (69·0% to 83·9%)	92/121 – 76·0% (67·7% to 82·8%)	160/187 – 85·6% (79·8% to 89·9%)	252/308 – 81·8% (77·1% to 85·7%)

Abbreviations: SUVmax= maximum standardised uptake value, DCE-CT= dynamic contrast-enhanced computed tomography.

Table 6: Costs and consequences results for base case analysis from a healthcare system perspective.

Single Outcomes	PET/CT	DCE-CT	DCE-CT /PET/CT
Cost	£4013 (206)	£3305 (199)	£4058 (210)
Accurately managed cases	82·0% (1·6%)	77·8% (2·0%)	84·4% (1·4%)
Malignancies treated	44·2% (2·5%)	40·1% (2·5%)	46·7% (2·4%)
QALYS	7·64 (0·25)	7·43 (0·26)	7·76 (0·24)
Life expectancy (years)	10·5 (0·32)	10·22 (0·34)	10·65 (0·31)
Delayed or no treatment	20·31% (1·84%)	25·63% (2·15%)	17·18% (1·59%)
Malignancies missed	16·2% (1·68%)	20·49% (2·04%)	13·71% (1·43%)
Benign cases treated	9·91% (1·25%)	9·8% (1·25%)	9·0% (1·23%)
Operative deaths	1·0% (0·05%)	0·92% (0·05%)	1·05% (0·05%)
Operative deaths for benign cases	0·17% (0·02%)	0·16% (0·02%)	0·15% (0·02%)
Operative deaths for malignant cases	0·96% (0·05%)	0·87% (0·05%)	1·01% (0·05%)

Values reported as Mean (SD).

Abbreviations: DCE-CT= Dynamic contrast-enhanced computed tomography **,** PET/CT=18Fluorine Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, QALYS= quality-adjusted life-year.

FIGURES

Figure 1: SPUtNIk trial STARD flowchart

Figure 2: ROC curves comparing PET/CT grading, SUVmax, peak enhancement and a combination of the variables

Aberviations: DCE-CT= Dynamic contrast-enhanced computed tomography, PET/CT=18Fluorine Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography. SUVmax= maximum standardised uptake value

Figure 3: Cost-effectiveness acceptability curves for the 3 imaging approaches for cost per correctly treated malignancy (A) and per correctly managed case (B).

Willingness to pay is expressed in £GBP. The x-axis represents the willingness to pay threshold for each correctly treated or diagnosed case, while the y axis represents the proportion of model iterations in which a particular imaging strategy is the most cost-effective approach at each of the willingness to pay thresholds. For example, below a willingness to pay threshold of £10,000, DCE-CT is the most cost-effective in 100% of model iterations.